

2/PRTS

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Process and apparatus for producing tablets

The present invention relates to a process and an apparatus for
5 producing tablets by melt extrusion.

European patent EP-B-0 240 906 discloses a process for producing
tablets by melt extrusion, in which an extrudable pharmaceutical
mixture is heated and extruded in the form of a continuous
10 product strip, the product strip which is still moldable is
compressed to a continuous tablet belt, the individual tablets in
the belt being connected together by product webs, the tablet
belt is allowed to cool, and the tablets are finally singulated
and deflashed.

15 In contrast to conventional processes which are based on the
compression of powders or granules, in the melt extrusion process
an active ingredient-containing melt of a thermoplastic,
water-soluble or water-swellable polymer is processed.

20 For this purpose, the individual components are first mixed and
then melted in an extruder. The mixing of the components may also
take place in the extruder. Suitable extruders are, for example,
single screw machines, intermeshing screw machines, multiscrew
25 extruders, especially twin screw extruders, which may be designed
to be corotating or counter-rotating and, where appropriate, may
be equipped with kneading disks. Suitable extruders are included,
for example, in the ZSK series from Werner & Pfleiderer.

30 The extruder may have a plurality of inlets. It is possible,
where appropriate, to provide separate addition of solid and
liquid ingredients of the mixture. It is additionally possible to
provide connectors for introducing inert gas and/or for
degassing. Since the mixing of the ingredients takes place in the
35 extruder, it is normally possible to dispense with premixing. The
heated pharmaceutical mixture is expelled in the form of product
strips or belts through one or more dies, for example slit dies,
in the extruder head. The product strips or belts are then sent
to shaping means. Various means for shaping tablets from active
40 ingredient-containing melts are known. For example, the melt can
be compressed to tablets by a calendering process using
counter-rotating molding rolls. In this case, depressions
corresponding to the desired tablet shape are provided in one or
in both molding rolls. However, it is also possible to allow a
45 belt having depressions or apertures of the desired tablet shape
to pass through between two smooth calender rolls. The tablet
belt produced by calendering contains the shaped individual

tablets, which are normally connected together by fine burrs or product webs. These product webs may in fact be useful in the shaping because they favor release of the tablet from the mold. Concerning the procedure for the conventional melt extrusion process, reference may be made not only to EP-B-0 240 906 but also to EP-B-0 240 904, EP-B-0 337 256 and EP-B-0 358 105.

To produce single tablets from the tablet belt shaped in this way, the belt is initially allowed to cool, and the cooled tablet belts are put into a large vessel, which is made to rotate. The mechanical stress arising thereby, which can be controlled within certain limits by the quantity of tablets added, the size of the vessel and its speed of rotation, leads to singulation of the large, plate-like parts of the tablet belt stepwise to ever smaller aggregates, until finally only a large proportion of so-called "twins" still remains, which is singulated to individual tablets as the process continues. Collision of the tablets during rotation in the vessel abrades off the residues of the burrs, so that the tablets are also deflashed simultaneously with the singulation.

The known process for producing single tablets by melt extrusion is, however, associated with disadvantages. Whereas the melt extrusion process provides a continuous process for producing tablets, the final singulation and deflashing process takes place batchwise in vessels. Since the processing time in the vessel, in particular for singulating the tablets from the tablet belt, is relatively long, the possible productivity of a continuous tablet production by melt extrusion is not exploited. In addition, it has emerged that this simple singulation and deflashing process in the vessel is not successful in all cases. In the particular case of tablets having a score to facilitate dividing, the known process leads to a high proportion of broken tablets, which must be rejected mechanically and considerably reduce the yield. Divisible tablets having a score have, however, in recent years become increasingly frequently employed because it is possible with them to adapt the dose, e.g. pediatric/adult dosage, with a single tablet.

It is an object of the present invention to provide a process for producing tablets by melt extrusion which firstly makes greater productivity possible and, moreover, ensures production of tablets which are easily broken, for example divisible tablets, without unacceptably high loss rates. Another object of the present invention is to provide an apparatus for carrying out the process.

We have found that this object is achieved by the process claimed in the main claim herein.

The present invention accordingly relates to a process for
5 producing tablets by melt extension in which, in a manner known per se, an extrudable, preferably pharmaceutical, mixture is heated and extruded in the form of a continuous product strip, the still deformable product strip is compressed to a continuous tablet belt, the individual tablets in the belt being connected
10 together by product webs, the tablet belt is allowed to cool, and the tablets are finally singulated and deflashed, wherein firstly the tablets are mechanically singulated in a continuous process, and then the singulated tablets are transported further and subsequently deflashed.

15 Accordingly, the invention proposes that the combined singulation and deflashing process which in known processes takes place in a cylindrical vessel be carried out in two separate steps, with the singulation process taking place continuously.

20 The process of the invention is associated with numerous advantages. A continuous singulation of the tablet belt to single tablets means that this step can take place at the same speed as the shaping of the tablets by melt extrusion. The subsequent
25 deflashing step can take place in a vessel as in the process of the invention. Preference is given to employment of coating vessels known per se or machines used for film coating (for example the Dria-Coater from Driam). Since it is no longer necessary for singulation to take place in the vessel, the time
30 required for deflashing therein is distinctly reduced. The overall result therefore is a saving in processing time compared with the known process.

The separation, provided according to the invention, of
35 singulation and deflashing additionally allows the two processes to be specifically adapted to particular requirements. Since it is now necessary in the concluding deflashing step in the vessel only to remove the residues of the burr present on the individual tablets, the deflashing can be carried out under milder
40 conditions. In the prior art process, the energy input into the vessel is considerably greater, because it is also necessary in particular for the singulation of the larger tablet plates to take place therein. The process of the invention can therefore be employed with particular advantage in particular in the
45 production of tablets which break easily, such as, for example, tablets with scores.

For singulation of the tablet belt by the process of the invention it is necessary to reduce the temperature of the tablets until there is no bending or deformation of the tablets, which may still be plastic, on exposure to a mechanical force.

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In an advantageous embodiment of the process of the invention, a force with a component perpendicular to the plane of the cooled tablet belt is allowed to act on the belt to singulate the tablets. This leads directly to a bending and subsequent breaking
10 of the tablet belt at the thin product webs which connect the individual tablets together. The process functions very efficiently in particular when the temperature of the tablet belt is low enough for the thin product webs or burrs no longer to be plastic, but to display a certain brittleness. However, it is
15 also possible to allow a force to act in the plane of the tablet belt, so that the tablets are torn apart at the product webs. This variant of the process of the invention can even be employed when the temperature of the tablet belt is still high enough for the product webs still to have a certain plasticity. However, a
20 particularly advantageous process is one in which there is both a force acting perpendicular to the tablet belt and a force acting in the plane of the tablet belt.

The perpendicular component of force is preferably generated by
25 diverting the solidified tablet belt out of its transport plane, while the parallel component of force is generated by exerting a traction force on the solidified tablet belt.

The present invention also relates to an apparatus for producing
30 tablets, in particular for carrying out the process of the invention described above. The apparatus of the invention comprises at least one extruder, means, downstream of the extruder, for shaping a tablet belt, first transport means, downstream of the shaping means, for the tablet belt and means
35 for singulating and deflashing the tablets. In the apparatus of the invention, the means for singulating and deflashing the tablets comprise at least one singulating means, arranged downstream of the first transport means, and at least one deflashing means, arranged downstream of the singulating means
40 and spatially separate therefrom. Suitable shaping means are primarily two molding rolls which can be pressed against one another, as described in the European patent EP-B-0 240 906 mentioned at the outset. The first transport means may be, for example, a conveyor belt which serves primarily for cooling the
45 pharmaceutical melt which has been compressed to a tablet belt.

The singulating means following the first transport means is particularly advantageously designed as roller arrangement. In a simple embodiment, the singulating means comprises at least one rotatable roller for diverting the tablet belt out of a transport plane of the first transport means. The melt, which is initially still plastic, solidifies on the first transport means so that the solidified tablet belt leaves the transport means in a plane defined by the latter. It is possible to arrange a rotatable roller immediately following the transport means, which roller diverts the rigid belt for example downwards and thus exerts the force, provided in the process of the invention, perpendicular to the table belt. This diversion is associated with breakage of the, now brittle, connecting webs between the tablets. In an advantageous embodiment of the apparatus of the invention, the singulating means is designed as two counter-rotating rollers which can be pressed against one another. One of the rollers rotates above and the other roller rotates beneath the tablet belt. The rollers can be designed to be driveable. The speed of rotation can be selected to be greater than the speed with which the tablet belt is transported on the first transport means, so that the rollers generate a traction force in the plane of the tablet belt. The rollers can be arranged so that the tangential plane of the slot through which the tablet belt passes forms an angle with the plane of the tablet belt on the transport means, so that once again diversion of the solidified belt is brought about, leading to breakage of the tablet belt at the product webs. The rollers or roller combinations used as singulating means can easily be adapted to the different requirements of specific tablet formulations. For example, it is possible to employ rollers differing in surface structure. It is possible to use, for example, smooth rollers, rollers with brushes or pins, with bars or other structures. The force applied for the singulation can be influenced by changing the arrangement of the rollers, the diameter of the rollers and the contact pressure. Other possibilities are different combinations of material, for example foams, plastics, rubber or stainless steel. It is possible in particular to influence the traction force in the plane of the tablet belt through the speed of rotation of the rollers.

In a preferred embodiment of the invention, the first transport means has additional means for cooling the extruded and shaped tablet belt. If the transport means is designed, for example, as circulating conveyor belt it is possible to provide one or more cooling plates underneath the upper part of the belt. The cooling can be adapted to the specific requirements of the particular tablet formulation through the length of the transport belt. With

longer transport belts it is possible to divide the cooling section into individual zones which are cooled separately, so that a stepwise, easily controlled cooling process can be carried out.

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The cooling provided for the first transport means can, however, also take place by air cooling. In this case, cooling from above is possible, for example with cooling air being allowed to pass over the shaped tablet belt. However, it is also possible to

- 10 design the transport belt with perforations and provide air cooling from below. Cooling of the tablet belt can, however, also take place, for example, by spraying with cooling water.

- In a particularly preferred embodiment of the apparatus of the
15 invention, a second transport means is provided between the singulation means and the deflashing means and comprises a shaking or vibrating unit. The latter can be designed, for example, as vibrating screen. After the singulation, the tablets fall onto a vibrating screen and are transported thereon to the
20 deflashing means. Larger residues of the burrs are removed from the tablets even on the vibrating screen, so that the processing time for the deflashing is further reduced. It is also possible for any "twins" still present after the singulation, that is to say two tablets still connected by product webs, to be separated
25 on the vibrating second transport means.

The present invention is explained in more detail below with reference to an example depicted in the drawings attached.

- 30 The drawings show:

Figure 1 a diagrammatic representation of an apparatus of the invention for producing single tablets by melt extrusion;

- 35 Figure 2 a plan view of a tablet belt immediately after shaping with the molding calender rolls; and

Figure 3 a section through the tablet belt of Fig. 2;

- 40 Figure 4 a plan view of a variant of the roller arrangement of the singulating means;

Figure 5 a plan view of another embodiment of the breaking roller of the singulating means.

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Figure 1 depicts an overall view of a preferred embodiment of the apparatus of the invention. The extruder 10, which is depicted diagrammatically, serves to mix and melt the pharmaceutical mixture. An extruder head 11 of the extruder 10 has a slit die 12 out of which the plastic extrudate is expelled in belt form. While still in the plastic state, the extrudate 13 reaches the shaping means 20 which, in the present case, is formed by two counter-rotating calender rolls 21, 23. Depressions 22 and 24, whose shape in each case corresponds to one half of the tablet to be produced, are formed in the surfaces of the rolls. The rolls are mutually adjusted so that in each case two halves of the shape coincide exactly in the contact region. In this contact region the rolls form an intake slit 25, which extrudate 13 enters and is compressed to a tablet belt 14.

The tablet belt produced in this way is depicted in more detail in Figures 2 and 3. The tablets 15 in the tablet belt 14 are connected together by product webs 16. As is evident in particular from the sectional depiction in Figure 3, the product webs 16 are very thin compared with the tablets 15.

The tablet belt reaches, where appropriate via suitable deflecting devices 17, a first transport means 30 which, in the present case, is designed as belt conveyor unit. The conveyor unit has a circulating conveyor belt 31 and two deflecting rolls 32, 33. In the example depicted there is also provision of cooling means 70, with depiction by way of example of a circulating air cooling 71 with a cooling unit 72 above the tablet belt 14 and cooling plates 73 below the tablet belt 14.

The length of the conveyor belt 31 is chosen - depending on the additional cooling means used - so that at the end of the conveyor belt the product webs 16 have cooled so much that they already have a certain brittleness. The substantially solidified tablet belt on the transport means 30 defines a transport plane 34 - depicted by a broken line in Figure 1.

The singulating means 40 immediately follows the first transport means 30 and consists in the present case of two rollers 41, 42 pressed against one another. The upper roller 41 is designed as embossed roller, while the lower roller is designed as smooth roller. The rollers are displaced slightly relative to one another in the direction of transport of the belt and are, moreover, arranged so that the slit 43 defined by the rollers is located below the transport plane 34 of the solidified belt. It is evident that the tangential plane 44 - depicted by a broken line - of the slit 43 forms an angle with the transport plane 34,

so that it is clear that the solidified band is diverted downward on being guided through the slit 43. This diversion exerts a force essentially perpendicular to the plane of the tablet belt 14, which causes the thin product webs 16 to break. In the 5 example depicted, there is also a guide device 45 provided for the tablet belt between the two rollers 41 and 42 and the end of the conveyor belt 31.

After passing through the singulating means, the tablets of the 10 belt are in the form of single tablets 18, some of which still have residues of the product web on the periphery. The individual tablets 18 fall onto a second transport means 16, which is designed in this case as a shaking screen 61. The shaking screen 61 guides the individual tablets 18 into the deflashing means 50, 15 which consists of a rotating drum 52 with inlet opening 51. During transport on the shaking screen 61, the residues of the product webs are broken off the individual tablets 18 and enter a collecting channel 62. The flash present on the tablets is therefore now only very thin and is completely abraded off after 20 a short treatment time in the drum 52.

Figure 4 shows another variant of the roller combination of the invention for the singulating means 40. The roller 46 rotating above the tablet belt has longitudinal bars 47, while the lower 25 roller 48 has transverse bars 49 which are arranged essentially perpendicular to the longitudinal bars 47.

Figure 5, finally, shows another variant of a breaking roller for the singulating means 40'. The roller 46' has a plurality of 30 flexible thin plastic plates 47' oriented along the axis of the roller 46'. The thin plates may be, for example, bonded or molded onto the basic cylindrical element of the roller, or be secured in slots formed therein. The thin plate roller 46' can be employed as single breaking roller or together with a 35 counter-roller of similar construction or a smooth roller.

The term "tablet" is intended for the purpose of the present invention to have the widest possible meaning. It is linked neither to a particular shape nor to a particular application. It 40 therefore encompasses, for example, tablets for oral use, but also tablets for example for rectal use in the form of suppositories. In this connection, tablets also mean all dosage forms suitable for use as pharmaceuticals, crop treatment compositions, and human and animal foodstuffs, and for releasing 45 fragrances and perfume oils.

Active pharmaceutical ingredients for the purpose of the invention mean all substances with a pharmaceutical action and minimal side effects as long as they do not decompose under the processing conditions. The amount of active ingredient per dose unit and the concentration may vary within wide limits depending on the efficacy and rate of release. The only condition in this connection is that they suffice to achieve their desired effect. Thus, the active ingredient concentration can be in the range from 0.1 to 95, preferably from 20 to 80, in particular from 30 to 70, percent by weight. The term active ingredient also encompasses in the present connection any combinations of active ingredients. Vitamins, for example, as also active ingredients for a purpose of the invention. Particularly preferred active ingredients are ibuprofen (as racemate, enantiomer or enriched enantiomer), ketoprofen, flurbiprofen, acetylsalicylic acid, verapamil, paracetamol, nifedipine and captopril.

The polymeric binder must soften or melt in the complete mixture of all the components in the range from 50 to 180°C, preferably 60 to 130°C. The glass transition temperature of the mixture must therefore be below 180°C, preferably below 130°C. If necessary, it is reduced by conventional, pharmacologically acceptable plasticizing excipients. Suitable polymeric binders are described, for example, in WO 97/15291.

Polymeric binders preferably employed for the melt extrusion of active pharmaceutical ingredients are: polymers or copolymers of N-vinylpyrrolidone, Eudragit types (acrylic resins) or celluloses. Particular preference is given in this connection to: polyvinylpyrrolidone (PVP), copolymers of N-vinylpyrrolidone and vinyl esters such as vinyl acetate, poly(hydroxyalkyl acrylates), poly(hydroxyalkyl methacrylates), polyacrylates, polymethacrylates, alkylcelluloses or hydroxyalkylcelluloses.

The extrudable mixture may, besides the polymeric binder and the active ingredient(s), also contain conventional additives, for example plasticizers, lubricants, flow regulators, dyes, stabilizers or wetting agents, preservatives, disintegrants, adsorbents, mold release agents and blowing agents. It is likewise possible for conventional pharmaceutical excipients, for example extenders and fillers, to be present. Suitable additives and pharmaceutical excipients are described, for example, in WO 97/15291.

Examples

Comparative example 1

- 5 A mixture containing 48% by weight of verapamil hydrochloride as active ingredient and hydroxypropylcellulose, methylhydroxypropylcellulose and lecithin powder as excipients was processed in a twin screw extruder (ZSK-58; Werner und Pfleiderer) to a homogeneous melt. The melt throughput was 120 kg/h. The material
- 10 temperature shortly before the die of the extruder was about 120-130°C. The melt was discharged through a slot die in the form of a sheet and shaped in a downstream molding roll calender to elongate tablets (without score, about 20 mm long, about 5 mm thick). The tablets left the calender in the form of a coherent
- 15 tablet belt. The tablet belts cooled on a transport belt with a total length of about 4 m through radiation of heat to the surrounding air.

- At the end of the transport belt, 50 kg of the resulting tablet
- 20 belt were broken down manually into smaller pieces of belt which were then introduced into a Driacoater pan (from Driam). The singulation and deflashing took place with the drum rotating at 20 rpm. The entire process took about 40 minutes. It was possible to singulate and deflash all the tablets.

25 Comparative example 2

- The test took place as indicated in comparative example 1, but the calendering resulted in elongate tablets (identical
- 30 length/width) with a score in the middle of the tablet. The singulation and deflashing in the Driacoater resulted in about 10-30% of the tablets being broken even during the rotation in the Driacoater.

35 Example 1

The test took place as indicated in comparative example 1, but with the following alterations:

- 40 - The transport belt contained at the end a brush roller (diameter about 9 cm) which was driven by a separate driving motor. The speed of rotation of the breaking rollers was adjusted to suit the conveying speed of the transport belt.
- 45 - The calendering resulted in breakable tablets having a score in the middle (score geometry as in comparative example 2).

Satisfactory singulation of the tablet belts was possible with the aid of the brush rollers. 50 kg of the singulated tablets were then put in a Driacoater and deflashed with the drum rotating at 5-10 rpm. Deflashing was complete after only 5 10 minutes. There was no detectable increase in the proportion of broken tablets.

Example 2

- 10 The test took place as indicated in example 1, but in place of a brush roller at the end of the transport belt there was a plastic roller 450 mm long with 9 thin plates oriented in the long axis of the roller (corresponding to the depiction in figure 5). The basic element of the cylindrical roller, which consisted of POM, 15 had a diameter of 75 mm. The thin plates were made of flexible PVC, were inserted about 15 mm deep into the roller element and projected about 20 mm beyond the surface of the roller.

- Satisfactory singulation of the belts of tablets with scores was 20 possible with the aid of the thin plate rollers. 400 kg of the singulated tablets were then put in a Driacoater and deflashed with the drum rotating at 5-10 rpm. Once again, there was no detectable increase in the proportion of broken tablets.

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